Regulation of Na,K-ATPase in the Diabetic Heart

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Diabetic cardiomyopathy (DCM) is a disorder that develops in the time course of diabetic disease. DCM is manifested by depressed cardiac performance (1) resulting from numerous metabolic abnormalities that besides altered cellular carbohydrate and energy metabolism (1) also involve defective function of the myocardial membrane receptors, signal transduction and ionic transport systems including those responsible for calcium handling (2–5). During the development of DCM hearts gradulally become less senstive to external stimuli mediated by catecholamines, calcium (6, 7), reactive oxygen species, ischemia (8) and ischemia/reperfusion injury (9). These perturbations have been found to be associated with a specific modulation of activity and properties of the heart sarcolemmal Na,K-ATPase. The latter was characterized by a moderate, 20-30 % decrease in the activity of the enzyme that was, however, accompanied by a marked preservation of its kinetic properties, particularly of the sensitivity of the Na,K-ATPase to stimulation by increasing concentrations of Na^+ and K^+ ions. Unchanged V_{max} and S_{50} for Na^+ and K^+ persisted even under conditions of the calcium paradox (CaP) in diabetic hearts (3). Our earlier findings (10) indicate that this presetvation of the Na,K-ATPase could be considered to be the main reason, leading to a survival of more than 83 % of cardiomyopathic rat hearts after CaP, in comparison to a complete failure of normal hearts (1, 11). Investigation of processes associated with preservation of specific properties and function of the sarcolemmal Na,K-ATPase in hearts of cardiomyopathic rats revealed an increase in the rate of non-enzymatic glycation of proteins leading to increased formation of fructosamines and followed by advanced Maillard products and protein crosslinks creation. Moreover, fructosamines formed abundantly in the sarcolemma of cardiomyopathic rat hearts represented a special source for an acceleration of free radical formation that was documented by elevated malondialdehyde content (5). Rising free radicals increased in turn the rigidity and altered the order-parameters of the sarcolemmal membrane phospholipids (11). The interrelated processes of non-enzymatic glycation of proteins and free radical production proved to play a key role in the regulation of properties and function of the sarcolemmal Na,K-ATPase, associated with an increased resistance of the diabetic hearts to calcium (11). Oppositely, a prevention of non-enzymatic glycation and the related free radical formation by resorcylidene aminoguanidine application also prevented the development of Ca-resistance in the diabetic hearts (11, 12), i. e. an adaptation process determined to protect the diabetic heart from the entry of that amounts of Ca^{2+} that would exceed the capacity of the defective intracellular calcium handling (12, 13). However, besides the described regulation of activity and function of the Na,K-ATPase operating actually in the myocytes, the enzyme in the diabetic hearts is also regulated by the mechanisms controlling its actual quantity including its expression, as well as by its a-subunit isoform composition. A decrease in Na,K-ATPase concentration in skeletal muscles and particularly in the heart ventricular muscles of diabetic rats was already reported by Kjeldsen et al (14). Our recent unpublished results, obtained in cooperation with the group of Kjeldsen in Copenhagen, confirmed this finding. Moreover, they indicate that when expressed in per cent of the amount and activity of Na,K-ATPase in the hearts of parallelly kept and weight matching healthy control rats, the relative decrease of enzyme concentration in the heart tissue was similar to the decrease in its activity as estimated in the isolated, partially purified heart sarcolemmal fraction. In spite of all limitations for such a comparison, the latter points to probable diabetes-induced alterations in a-subunit isoform pattern of the cardiac Na,K-ATPase – a possibility, that is now under investigation.

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